

At page 20, delete Table 3 and insert the following:

Name	aa ¹	aa ² aa ³	aa ⁴	aa ⁵	X	P	Y	aa ⁶	aa ⁷	aa ⁸ aa ⁹	aa ¹⁰	S ²	Seq ID
PAI-2	K	D		B		TG <u>R</u> TG		P			K	GY	1
PAI-2(b)	K	D	P	P		TGRTG		P	P		K	GY	2
DEVD	K	D		B		DEVD <u>G</u> ID		P			K	GY	3
DevN	K	D		B		DEV <u>N</u> GID		P			K	GY	4
PARP	K	D		B		EVD <u>G</u> ID		P			K	GY	5
ICE	K	DY		B		AD <u>G</u> ID		P			K	GY	6
Fm-DEVD	Fm -K	D		B		DEVD <u>G</u> ID		P			K	GY	7
Fm-DEVN	Fm -K	D		B		DEV <u>N</u> GID		P			K	GY	8
Fm-PARP	Fm -K	D		B		EVD <u>G</u> ID		P			K	GY	9
Fm-KNFES	Fm -K	D				AIP <u>M</u> SI		P			K	GY	10
	Fm -K	D				AIP <u>N</u> uSI		P			K	GY	11
Fm-G2D2D	Fm -K	D		B		GDEV <u>D</u> GID	G	P			K	GY	12
Fm-CGD2D	Fm -K	D		B	J	GDEV <u>D</u> GID	GJ	P			K	GY	13
Z-CGD2D	Z- K	D		B	J	GDEV <u>D</u> GID	GJ	P			K	GY	14
Fm-ICE	Fm -K	DY		B		AD <u>G</u> ID		P			K	GY	15

At pages 21, please delete Table 4 and insert the following:

Substrate class	aa ¹	aa ² aa ³	aa ⁴	aa ⁵	X	P	Y	aa ⁶	aa ⁷	aa ⁸	aa ⁹	aa ¹⁰	S ²	Seq ID
CPP32 substrates (preferably with DER and TMR fluorophores). Note where Fmoc (Fm) is indicated, it is optional, and where not indicated it can be added.														
	Fa-K	D		P	JG	DEV DGIN	GJ	P					K	GY 16
	Fm-K	D		P	JG	DEV DGIN	GJ	P					K amide	17

	Fm-K	D		P	JG	(d-O)DEV \underline{D} GIN	GJ	P		K	GY	18
	Fm-K	D		P	JG	DEV \underline{D} GIN	G	P		K	GY	19
	Fm-K	D		P	G	DEV \underline{D} GIN	GJ	P		K	GY	20
	Fm-K	D		P	JG	DEV \underline{D} GID	GJ	P		K		21
										amide		
	Fm-K	D		P	JG	EEVEGIN	GJ	P		K	GY	22
	Fm-K	D		P	JG	D(dF)VDGIN	GJ	P		K	GY	23
	Fm-K	D		P	JG	(d-D)EV(d-D)GIN	GJ	P		K	GY	24
	Fm-K	D		P	JG	DEV \underline{D} GIN	GJ	P		K	GY	25
	Fm-K	DB			JG	DEV \underline{N} GIN	GJ	P		K	GY	26
	Fm-K	DB			JG	DEV \underline{D} GID	GJ	P		K	GY	27
	Fm-K	DB			JG	DEV \underline{D} GIN	GJ	P		K	GY	28
	Fm-K	DB			JG	DEV \underline{N} GID	GJ	P		K	GY	29
	K	D		B	JJ	GDEV \underline{D} GID	JJ	P		K	GY	30
	K	D		B	J	GNEV \underline{D} GID	GJ	P		K	GY	31
	K	D		B	J	GDEV \underline{D} GIN	GJ	P		K	GY	32
	K	D		B	J	GNEV \underline{D} GIN	GJ	P		K	GY	33
	K	D		B	J	GDEV \underline{N} GIN	GJ	P		K	GY	34
	K	D		B	J	GNEV \underline{N} GIN	GJ	P		K	GY	35
	K	D		B	JG	ODEV \underline{D} GID	GJ	P		K	GK	36
	K	D		B	JG	dODEV \underline{D} GID	GJ	P		K	GY	37
	K	D		B	JG	WDEV \underline{D} GID	GJ	P		K	GY	38
	K	D		B	JG	dWDEV \underline{D} GID	GJ	P		K	GY	39
	K	D		B	JG	dOdODEV \underline{D} GID	GJ	P		K	GY	40
	K	D		B	JG	dWdWDEV \underline{D} GI D	GJ	P		K	GY	41
	K	D		B		YVAD \underline{G} ID		P		K	GY	42
	K	D		B		YVAD \underline{G} IN		P		K	GY	43
	K	D		B		YV \underline{A} GIN		P		K	GY	44
	K	D		B	G	YVAD \underline{G} ID	G	P		K	GY	45
	K	D		B	G	YVAD \underline{G} IN	G	P		K	GY	46

02
cont.

Handwritten notes: A2, Comp

	K	D		B	G	YVANGIN	G	P			K	GY	47
	K	D		B	JG	YVADGID	GJ	P			K	GY	48
	K	D		B	JG	YVANGID	GJ	P			K	GY	49
	K	D		B	JG	YVANGIN	GJ	P			K	GY	50
	K	D		B	JG	YVADGIN	GJ	P			K	GY	51
	K	D		B	JG	dYVADGIN	GJ	P			K	GY	52
LAMIN-A													
	Fm-K	D		P	JG	LVEIDNG	J	P			K	GY	53
	FM-K	DP			JG	LVEIENG	J	P			K	GY	54
	K	D		B		LVEIDNG		P			K	GY	55
	K	D		B	G	LVEIDNG	G	P			K	GY	56
	K	D		B	JG	LVEIDNG	GJ	P			K	GY	57
	K	D		B	JG	LVEINNG	GJ	P			K	GY	58
ProCPP32Asp175													
	Fm-K	D		P	J	GIETESGV	GJ	P			K	GY	59
	Fm-K	D		P	J	GIETDSG	J	P			K	GY	60
	Fm-K	D		P	J	GIETESG	J	P			K	GY	61
	K	D		B		GIETDSGVDD		P			K	GY	62
	K	D		B		GIETNSGVDD		P			K	GY	63
	K	D		B	G	GIETDSGVDD	G	P			K	GY	64
	K	D		B	G	GIETNSGV	G	P			K	GY	65
	K	D		B	J	GIETDSGV	J	P			K	GY	66
	K	D		B	J	GIETNSGV	J	P			K	GY	67
	K	D		B	JG	GIETDSGV	GJ	P			K	GY	68
	K	D		B	JG	GIETNSGV	GJ	P			K	GY	69
ProCPP32Asp28													
	K	D		B		GSESMDSGISL D		P			K	GY	70
	K	D		B	G	GSESMDSG	G	P			K	GY	71
	K	D		B	JG	GSESMDSG	GJ	P			K	GY	72
NS3 NS5A/5B													
	K	D		B	JG	DVVCCSMS	GJ	P			K	GY	73
	K	D		B	JG	DVVCDSMS	GJ	P			K	GY	74
	K	D		B	JG	DVVCCSdMS	GJ	P			K	GY	75
	K	D		B	JG	DVVCDSdMS	GJ	P			K	GY	76

Q2

Conf.

K	D		B	JG	DVVCCP <u>d</u> MS	GJ	P			K	GY	77
K	D		B	JG	EDVVCC <u>S</u>	GJ	P			K	GY	78
K	D		B	JG	EDVVCD <u>S</u>	GJ	P			K	GY	79
K	D		B	JG	EDdVVCC <u>P</u>	GJ	P			K	GY	80
K	D		B	JG	EDdVVCD <u>P</u>	GJ	P			K	GY	81
K	D		B	JG	DdVVCC <u>S</u> dMS	GJ	P			K	GY	82
K	D		B	JG	DVdVCD <u>S</u> dMS	GJ	P			K	GY	83
K	D		B	JG	DdVVCC <u>P</u> dMS	GJ	P			K	GY	84
K	D		B	JG	DVVCC <u>S</u> M	GJ	P			K	GY	85
K	D		B	JG	DVVCD <u>S</u> M	GJ	P			K	GY	86
K	D		B	JG	VCC <u>S</u> M	GJ	P			K	GY	87
K	D		B	JG	VC <u>D</u> S	GJ	P			K	GY	88

NS3 NS4A/4B

K	D		B	JG	DEMEEC <u>S</u> QHL		P			K	GY	89
K	D		B	JG	DEMEEC <u>P</u> QHL		P			K	GY	90
K	D		B	JG	DEMEED <u>S</u> QHL		P			K	GY	91
K	D		B	JG	EMEEC <u>S</u> QHL		P			K	GY	92
K	D		B	JG	EMEEC <u>P</u> QHL		P			K	GY	93
K	D		B	JG	EMEED <u>S</u> QHL		P			K	GY	94
K	D		B	JG	EMEEC <u>S</u> QHL	G	P			K	GY	95
K	D		B	JG	EMEEC <u>P</u> QHL	G	P			K	GY	96
K	D		B	JG	EMEED <u>S</u> QHL	G	P			K	GY	97
K	D		B	JG	EMEEC <u>S</u> QHL	GJ	P			K	GY	98
K	D		B	JG	EMEEC <u>P</u> QHL	GJ	P			K	GY	99
K	D		B	JG	EMEED <u>S</u> QHL	GJ	P			K	GY	100

Ext. PAI-2

K	D		B	JG	VMTG <u>R</u> TG	J	P			K	GY	101
K	D		B	JG	VdMTG <u>R</u> TG	J	P			K	GY	102
K	D		B	JG	VMTG <u>R</u> TG	J	P			K	GY	103
K	D		B	JG	VMTG <u>R</u> TG	J	P			K	GY	104

THROMB

K	D		B	JG	VMTG <u>R</u> G	J	P			K	GY	105
K	D		B	JG	VMTG <u>R</u> G	GJ	P			K	GY	106
K	D		B	JG	VdmTG <u>R</u> G	GJ	P			K	GY	107

Urokinase

a2
cont.

	Fm-K	D		P	J	TGRT								108
		Fm-D		P		TGRT	G	P			K	GY		109
	Fm-K	D		P		VMTGRT	GJ	P			K	GY		110
	Fm-K	D		P		TGRT	GJ	P			K	GY		111
	Fm-K	D		P	JG	TGRT	GJ	P			K	GY		112
	Fm-K	D		P	JG	TGRT	G	P			K	GY		113
	Fm-K	D		P	G	TGRT	G	P			K	GY		114
	K	D		P	J	TGRTG	J	P			K	GY		115
	K	D		P	C3	TGRTG		P			K	GY		116
	K	D		P	C7	TGRTG		P			K	GY		117
	K	D		B	JG	VMTGRVG	J	P			K	GY		118
	K	D		B	JG	VdMTGRVG	J	P			K	GY		119
F12A														
	K	D		B	JG	VMTGRAG	J	P			K	GY		120
	K	D		B	JG	VdMTGRAG	J	P			K	GY		121
Swedish KM/NL AMLOID														
	Fm-K	D		P	JG	SEVKLDAEF GC5PKGY	GJ	P			K	GY		122
	Fm-K	D		P	JG	S(d-E)VK(d-L) DAE(d-F)	GJ	P			K	GY		123
	Fm-K	D		P	JG	S(d-E)VK(d-L) DAE(d-F)	GJ	P			K	GY		124
	K	D		B	JG	SEVNLD AEF	GJ	P			K	DD Y		125
	K	D		B	JG	SEVKLDAEF	GJ	P			K	DD Y		126
NATIVE AMYLOID														
	K	D		B	JG	SEVKMD AEF	GJ	P			K	DD Y		127
CATHESPSIN G														
	K	D		B	JG	SEVKMDDEF	GJ	P			K	DD Y		128
	K	D		B	JG	SEVNLDDEF	GJ	P			K	DD Y		129
APP[709-710]														
	K	D		B	JG	GVVIATVIVIT	GJ	P			K	DD Y		130

APP[708-719]

	K	D		B	JG	YGVVIATVIVIT	GJ	P			K	DD Y	131
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APP[711-716]

	K	D		B	JG	VIATVI	GJ	P			K	DD Y	132
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APP[708-713]

	K	D		B	JB	YGVVIA	GJ	P			K	DD Y	133
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PSA Sg1

	K	D		B	JJ	QQLLHN	JJ	P			K		134
	K	D		B	JG	QQLLHN	GJ	P			K		135
	K	D		B	G	QQLLHN	G	P			K		136
	K	D		B		QQLLHN		P			K		137

PSA Sg2

	K	D		B	JJ	SIQYTY	JJ	P			K		138
	K	D		B	JG	SIQYTY	GJ	P			K		139
	K	D		B	G	SIQYTY	G	P			K		140
	K	D		B		SIQYTY		P			K		141

PSA Sg3

	K	D		B	JJ	SSQYSN	JJ	P			K		142
	K	D		B	JG	SSQYSN	GJ	P			K		143
	K	D		B	G	SSQYSN	G	P			K		144
	K	D		B		SSQYSN		P			K		145

PSA Sg4

	K	D		B	JJ	SSIYSQ	JJ	P			K		146
	K	D		B	JG	SSIYSQ	GJ	P			K		147
	K	D		B	G	SSIYSQ	G	P			K		148
	K	D		B		SSIYSQ		P			K		149

Cathepsin D substrates (preferably with diethylrhodamine fluorophore, note fmoc (Fm) is optional)

	Fm-K	D		P	JG	SEVNLD AEF	GJ	P			K	GY	150
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Caspase-9

	Fm-K	D		P	JG	LEHDGIN	GJ	P			K	GY	151
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Caspase-8

	Fm-K	D		P	JG	LET DGIN	GJ	P			K	GY	152
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Caspase-1

A2
Conclude

	Fm-K	D		P	JG	WEHDGIN	GJ	P			K	GY	153
	Fm-K	D		P	JG	YVHDG	J	P			K	GY	154
	Fm-K	D		P	JG	YVHDGIN	GJ	P			K	GY	155
	Fm-K	D		P	JG	YVHDA		P			K	GY	156
Granzyme B													
	Fm-K	DP			JG	IEPDS	GJ	P			K	GY	157
Collagenase													
	Fm-K	DP			JG	PLGIAGI	GJ	P			K	GY	158
HIV-1 protease													
	Fm-K	DP			JG	SQNYPIVQ	GJ	P			K	GY	159
Hepatitis C protease													
	Fm-K	DP			JG	EDVVCCS	GJ	P			K	GY	160

Delete the paragraph at page 37, lines 15-22 and substitute therefor the following:

A3

When it is desired to link the indicator to a solid support through the peptide backbone, the peptide backbone may comprise an additional peptide spacer (designated S¹ or S² in Formula I). The spacer may be present at either the amino or carboxyl terminus of the peptide backbone and may vary from about 1 to about 50 amino acids, more preferably from 1 to about 20 and most preferably from 1 to about 10 amino acids in length. Particularly preferred spacers include Asp-Gly-Ser-Gly-Gly-Gly-Glu-Asp-Glu-Lys (SEQ ID NO:161), Lys-Glu-Asp-Gly-Gly-Asp-Lys (SEQ ID NO:162), Asp-Gly-Ser-Gly-Glu-Asp-Glu-Lys (SEQ ID NO:163), and Lys-Glu-Asp-Glu-Gly-Ser-Gly-Asp-Lys (SEQ ID NO:164).

Delete the paragraph at page 52, lines 13-21 and substitute therefor the following:

A4
Ha3

Fluorophores were linked to the amino terminus via the α -amino group of aspartic acid residue (D) and to the ϵ -amino group of lysine (K). Labeling was accomplished by the displacement of a succinimidyl group linked to 6-TMR or DER. The structure of the peptide, called NorFES-KGY is:

Fluorophore1-DAIPNleSIPKGY

Fluorophore2

(SEQ ID NO:165)

Delete the paragraph at page 55, lines 7-15 and insert the following:

21/04/25
AS
In addition, we have synthesized and derivatized (homodoubly-labeled) PAI-2, CS-1 (a 31 residue long peptide) and two DEVD-like peptides that did not allow the dye-dye dimer formation. The CS-1 peptide shows that in a significantly longer peptide the dye-dye dimer structure can be formed. Note this peptide contains four proline residues in the amino terminal side of the putative cleavage site Ile-Leu bond. There is one proline in the carboxyl domain also. The results from the CS-1 peptide support a potentially larger sequence between the two dyes (fluorophores). Two DEVD-like peptide's amino acid sequences that did not allow the formation of productive H-type dimers are F₁-DEVDGIDPK[F₁]GY (SEQ ID NO:166) and F₁-PDEVDGIDPK[F₁]GY (SEQ ID NO:167).

Delete Table 12 at page 55, line 32 through page 56, line 1 and insert the following:

94
1/05

	Structure	Cellular uptake/ magnitude	Uptake checked by	Seq ID NO
1	Fm-K[F ₁] DAIPNluSIPK[F ₁]GY	Yes/high	FM	168
2	K[F ₁] DAIPNluSIPK[F ₁]GY	Yes/weak	FM	169
3	Fm-DAIPNluSIPK[F ₁]GY	No/	FM	170
4	Fm-K[F ₁]DBDEVDGIDPK[F ₁]GY	Yes/high	FM & FC	171
5	K[F ₁]DBDEVDGIDPK[F ₁]GY	Yes/weak	FM	172
6	Fm-K[F ₁]DBDEVNGIDPK[F ₁]GY	Yes/high	FM	173
7	K[F ₁]DBDEVNGIDPK[F ₁]GY	Yes/weak	FM & H	174
8	Fm-K[F ₁]DBEVDGIDPK[F ₁]GY	Yes/high	FM & FC	175
9	K[F ₁]DYBADGIDPK[F ₁]GY	Yes/weak	FM	176
10	Fm-K[F ₁]DBGDEVDGIDGPK[F ₁]GY	Yes/high	H & FC	177
11	Fm-K[F ₁]DBJGDEVDGIDGPK[F ₁]GY	Yes/high	FC	178
12	Z-K[F ₁]DBJGDEVDGIDGPK[F ₁]GY	Yes/weak	FM	179
13	Fm-K[F ₁]DYBADGIDPK[F ₁]GY	Yes/high	FM	180
14	K[F ₁]DBEVDGIDPK[F ₁]GY	Yes/weak	FM	181

Delete the paragraph at page 57, lines 10-21 and insert the following:

9/11/07
a7

The elastase substrate, Fm-K[F1]DAIPNluSIPK[F1]GY, (SEQ ID NO:182, where F1 was carboxytetramethylrhodamine, Fm was Fmoc, K[F1] was F1 covalently attached through the epsilon amino group of lysine (K), and Fm-K is the Fmoc group covalently attached at the alpha amino group of the amino terminal lysine residue) was used with HL-60 cells. Cells were incubated with various concentrations of elastase substrate ranging from 10 nM to 10 μ M for 5 minutes to 60 minutes. Then the cells were diluted 5-fold with RPMI 1640 medium containing 5% serum or with phosphate buffered saline. The samples were centrifuged and washed once more with 1 ml of washing solution. After centrifugation and removal of the washing solution, cell pellets were loosened with about 25 μ l of medium and these cells were transferred to a glass capillary. Capillary tubes were then placed on a glass microscope slide and examined under a fluorescence microscope using standard rhodamine filters.

Delete the paragraph at page 58, lines 6-23 and insert the following:

9/11/07
a8

Control cells without substrate incubation and the sample with the greatest expected fluorescence signals were used to set the instrument detector parameters. For example after 15 minutes incubation of Jurkat cells with substrate compound #11 Fm-CGD2D: Fm-K[F1]DBJGDEVDGIDGJPK[F1]GY (SEQ ID NO:183, where F1 was carboxytetramethylrhodamine; Fm was Fmoc, K[F1] was F1 covalently attached through the epsilon amino group of lysine (K), Nlu was norleucine, B was aminoisobutyric acid, and J was epsilon-aminocaproic acid) an increase of about 10 channels indicating cellular uptake of the substrates was measured. Note substrate #11 was not completely quenched. Hence, a small amount of background fluorescence would be expected from the intact substrate. Signals from the cells that had been activated with 1 μ g/ml of anti-Fas antibody, CH11 clone for 1 to 6 hours indicated an increase in peak channel number. As much as a ten-fold increase in fluorescence intensity was observed. When the cells were co-incubated with the CPP32 protease inhibitor ZVAD-fluoromethylketone at 50 μ M along with an apoptosis inducing agent, e.g., anti-Fas antibody, this observed increase in fluorescence intensity was eliminated. This indicated that the signal from compound 11 was due to the CPP32 protease activity which was inhibitable by ZVAD-FMK. Hence, the observed fluorescence intensity in each cell as determined by flow cytometric analysis served as a direct measure of the intracellular CPP32 protease activity.

Delete the paragraph at page 59, lines 18-27 and insert the following:

9/11/07
a9

Jurkat cells are normally grown in 10% fetal calf serum containing RPMI 1640, at 37°C in a 5% CO₂ atmosphere. When the serum content was dropped to 4%, the Jurkat cell growth rate not only slowed down but also a significant number of cells died within 36 hours. The cell density used was

acg
conclude
about 400,000 cell per ml. After 36 hours, control wells contained about 50% dead cells (trypan blue-positive cells), whereas the wells containing 0.1 or 1.0 μ M concentration of compound #11 (Table 12) "Fm-CGD2D" or Fm-K[F1]DBJGDEVGDGIDGJPK[F1]GY (SEQ ID NO:184) showed only 10% or 8% nonviable cells. Hence, compound #11 which exhibits efficient cellular uptake slowed down apoptosis in these Jurkat cells where it acted as a CPP32 protease inhibitor or a CPP32 activating protease inhibitor.

Delete the paragraph at page 61, line 26 though page 62, line 15 and insert the following:

Q10
acg
The parent compound Fm-DEVD has the following composition: Fmoc-K[F1]DBDEVDGIDPK[F1]GY (SEQ ID NO:185). The bold face underlined letters are the protease recognition sequence consisting of 7 amino acid residues. Compound #10 contains two glycine extensions at both ends of this protease recognition sequence. The central protease recognition domain now is 8 residues long GDEVDGID (SEQ ID NO:186), since the glycine residue at the amino terminus is a part of native sequence. The two glycine residues which are inherently more flexible than other amino acids, *e.g.*, alanine, provide less conformational constraint or, conversely, more flexibility than compound 4 (Table 12) and thereby permit greater flexion when combined with Aib or Pro residues. Additional insertion of amino caproic acid at both termini with five methylene groups in addition to the one present in glycine provides further relaxation of the constrained conformation and, thus, greater flexibility for the protease recognition domain, GDEVDGID (SEQ ID NO:186). This progression of flexibility resulted in an increased hydrolysis rate with the CPP32 protease since CPP32 recognizes a more flexible protease recognition domain than does elastase. Support for this statement is that the CPP32 protease cleavage site in the proform of its physiological substrate, poly(ADP-ribose) polymerase, PARP, is located between two well-folded domains. Hence, it is expected that such a protease cleavage site would not be rigidly held or its conformation would be expected to be less defined than the remaining molecule. Hence, in order to provide these structural features to the substrate, introduction of flexible residues such as glycine, epsilon amino caproic acid, beta alanine, and amino butyric acid would be expected to play important roles in regulating the backbone flexibility of the substrate's central protease recognition domain. These additional preferred residues for the conformation determining domain are also expected to provide the needed bend-inducing influence.

Delete the paragraph at page 62, lines 23-29 and insert the following:

Q11
Q11
These examples provide a tetrapeptide and a pentapeptide comprising Lys-Asp-Aib-Gly (SEQ ID NO:187) or Lys-Asp-Aib-Ahx-Gly (SEQ ID NO:188) where Ahx is epsilon amino caproic

acid (i.e. $\text{NH}_2\text{-(CH}_2)_5\text{-COOH}$). The fluorophore is attached to epsilon amino group of the lysine residue. The carboxyl terminal CDR domain is defined as a tripeptide Gly-Pro-Lys and a tetrapeptide Gly-Ahx-Pro-Lys (SEQ ID NO:189). The hydrolysis rate was increased by 3-fold between compounds 4 (Fm-DEVD: Fm-K[F1]DBDEVDGIDPK[F1]GY, SEQ ID NO:190) and 10 (Fm-G2D2D: Fm-K[F1]DBGDEVDGIDGPK[F1]GY, SEQ ID NO:191).

Delete the paragraph at page 62, lines 30-34 and insert the following:

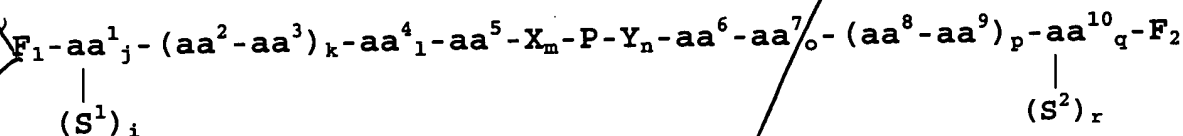
As illustrated in Figure 5, the hydrolysis rate was further increased by ca. 3-fold over the above glycine residue insertion with the amino caproic amino acid (Ahx) addition, compound 11 (Fm-CGD2D: Fm-K[F1]DB Ahx GDEVDGIDG Ahx PK[F1]GY, SEQ ID NO:192). Hence, overall at least a 9-fold increase in substrate hydrolysis rate was accomplished (compounds 4 and 11, Table 12).

In accordance with 37 CFR §1.121 a marked up version of the above-amended paragraph(s) illustrating the changes introduced by the forgoing amendment(s) are provided in Appendix B.

In the Claims:

Please amend the claims by substituting the following claims for the corresponding previously pending claims of the same number(s):

1. A fluorogenic composition for the detection of the activity of a protease, said composition having the formula:



wherein, P is a peptide selected from the group consisting of DEVDGIN (SEQ ID NO:193), (d-O)DEVDGIN (SEQ ID NO:194), DEVDGID (SEQ ID NO:195), LVEIDNG (SEQ ID NO:196), GIETESGV (SEQ ID NO:197), TGRT (SEQ ID NO:198), VMTGRT (SEQ ID NO:199), SEVKLDAEF (SEQ ID NO:200), S(d-E)VK(d-L)DAE(d-F) (SEQ ID NO:201), EDVVCCS (SEQ ID NO:202), EEVEGIN (SEQ ID NO:203), D(d-F)VDGIN (SEQ ID NO:204), (d-D)EV(d-D)GIN (SEQ ID NO:205), LVEIENG (SEQ ID NO:206), GIETDSG (SEQ ID NO:207), GIETESG (SEQ ID NO:208), LEHDGIN (SEQ ID NO:209), LETDGIN (SEQ ID NO:210), WEHDGIN (SEQ ID NO:211), YVHDG

(SEQ ID NO:212), YVHDGIN (SEQ ID NO:213), YVHDA (SEQ ID NO:214), TGRTG (SEQ ID NO:215), S(d-E)VK(d-L)DAE(d-F) (SEQ ID NO:216), IEPDS (SEQ ID NO:217), PLGIAGI (SEQ ID NO:218), SQNYPIVQ (SEQ ID NO:219);

F¹ and F² are fluorophores and F¹ is attached to the amino terminal amino acid and F² is attached to the carboxyl terminal amino acid;

S¹ and S², when present, are peptide spacers ranging in length from 1 to about 50 amino acids and S¹, when present, is attached to the amino terminal amino acid and S², when present, is attached to the carboxyl terminal amino acid;

i, j, k, l, m, n, o, p, q, and r are independently 0 or 1;

aa¹ and aa¹⁰ are independently selected from the group consisting of lysine, ornithine and cysteine;

aa², aa³, aa⁸, and aa⁹ are independently selected from the group consisting of an amino acid or a dipeptide consisting of Asp, Glu, Lys, Ornithine, Arg, Citulline, homocitrulline, Ser, homoserine, Thr, and Tyr;

aa⁵, aa⁴, aa⁶, and aa⁷ are independently selected from the group consisting of proline, 3,4-dehydropoline, hydroxyproline, alpha aminoisobutyric acid and N-methyl alanine;

X is selected from the group consisting of Gly, βAla, γAbu, Gly-Gly, Ahx, C7, βAla-Gly, βAla-βAla, γAbu-Gly, βAla-γAbu, Gly-Gly-Gly, γAbu-γAbu, Ahx-Gly, βAla-Gly-Gly, Ahx-βAla, βAla-βAla-Gly, Gly-Gly-Gly-Gly (SEQ ID NO:220), Ahx-γAbu, βAla-βAla-βAla, γAbu-βAla-Gly, γAbu-γAbu-Gly, Ahx-Ahx, γAbu-γAbu-βAla, and Ahx-Ahx-Gly;

Y is selected from the group consisting of Gly, βAla, γAbu, Gly-Gly, Ahx, C7, Gly-βAla, βAla-βAla, Gly-γAbu, γAbu-βAla, Gly-Gly-Gly, γAbu-γAbu, Gly-Ahx, Gly-Gly-βAla, βAla-Ahx, Gly-βAla-βAla, Gly-Gly-Gly-Gly, γAbu-Ahx, βAla-βAla-βAla, Gly-βAla-γAbu, Gly-γAbu-γAbu, Ahx-Ahx, βAla-γAbu-γAbu, and Gly-Ahx-Ahx;

when i is 1, S¹ is joined to aa¹ by a peptide bond through a terminal alpha amino group of aa¹; and when r is 1, S² is joined to aa¹⁰ by a peptide bond through a terminal alpha carboxyl group of aa¹⁰.

4. The composition of claim 1, having an amino acid sequence selected from the group consisting of Fa-KDPJGDEV D G I N G J P K G Y (SEQ ID NO:221), Fm-KDPJGDEV D G I N G J P k a m i d e (SEQ ID NO:222), Fm-KDPJG (d-O)DEV D G I N G J P K G Y (SEQ ID

argy
conclude

NO:223), Fm-KDPJGDEVDGINGPKGY (SEQ ID NO:224), Fm-KDPGDEVDGINGJPKGY (SEQ ID NO:225), Fm-KDPJGDEVDGIDGJPKamide (SEQ ID NO:226), Fm-KDPJGLVEIDNGJPKGY (SEQ ID NO:227), Fm-KDPJGIETESGVGJPKGY (SEQ ID NO:228), Fm-KDPJTGRGTGPKGY (SEQ ID NO:229), Fm-DPTGRTGPKGY (SEQ ID NO:230), Fm-KDPVMTGRTGJPKGY (SEQ ID NO:231), Fm-KDPTGRTGJPKGY (SEQ ID NO:232), Fm-KDPJGTGRTGJPKGY (SEQ ID NO:233), Fm-KDPJGTGRTGPKGY (SEQ ID NO:234), Fm-KDPGTGRTGPKGY (SEQ ID NO:235), Fm-KDPJGSEVKLDAEFGJPKGY (SEQ ID NO:236), Fm-KDPJGS (d-E)VK (d-L)DAE (d-F)GC5PKDDY (SEQ ID NO:237), Fa-KDPJGEDVVCCSGJPKGY (SEQ ID NO:238), KDPJGEEVEGINGJPKGY (SEQ ID NO:239), KDPJGD (d-F)VDGINGJPKGY (SEQ ID NO:240), KDPJG (d-D)EV (d-D)GINGJPKGY (SEQ ID NO:241), KDPJGLVEIENGJPKGY (SEQ ID NO:242), KDPJGIETDSGJPKGY (SEQ ID NO:243), KDPJGIETESGJPKGY (SEQ ID NO:244), KDPJGLEHDDGINGJPKGY (SEQ ID NO:245), KDPJGLETDDGINGJPKGY (SEQ ID NO:246), KDPJGWEHDDGINGJPKGY (SEQ ID NO:247), KDPJGYVHDGJPKGY (SEQ ID NO:248), KDPJGYVHDGINGJPKGY (SEQ ID NO:249), KDPJGYVHDAPKGY (SEQ ID NO:250), KDPJTGRGTGJPKGY (SEQ ID NO:251), KDPC3TGRGTGPKGY (SEQ ID NO:252), KDPC7TGRGTGPKGY (SEQ ID NO:253), KDPC5GS(d-E)VK(d-L)DAE(d-F)GJPKGY (SEQ ID NO:254), KDPJGIEPD SGJPKGY (SEQ ID NO:255), KDPJGPLGIAGIGJPKGY (SEQ ID NO:256), and KDPJGSQNYPIVQGJPKGY (SEQ ID NO:257).

These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position. In accordance with the requirements of 37 C.F.R. § 1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

REMARKS

This amendment is provided in Response to the Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant(s) request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a floppy disk containing the sequences (SEQ ID NOs: 1-257) in